PRODUCT MONOGRAPH

DOPAMINE HYDROCHLORIDE AND 5% DEXTROSE INJECTION, USP

Dopamine Hydrochloride 800, 1600, and 3200 µg/mL and 5% Dextrose
in VIAFLEX Plastic Container

Sympathomimetic

Baxter Corporation
Mississauga, ON
Canada L5N 0C2

Date of Revision:
April 24, 2013

Submission Control No: 161802

Table of Contents

DOPAMINE HYDROCHLORIDE AND 5% DEXTROSE INJECTION, USP

Dopamine Hydrochloride 800, 1600, and 3200 µg/mL and 5% Dextrose
in VIAFLEX Plastic Container

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous injection	Solution / 800 µg/mL, 1600 µg/mL and 3200 µg/mL	Sodium bisulfite. *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Dopamine hydrochloride is indicated for the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarction, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Where appropriate, restoration of blood volume with a suitable plasma expander, or whole blood should be instituted or completed prior to administration of dopamine hydrochloride.

Patients most likely to respond adequately to dopamine hydrochloride are those in whom physiological parameters, such as urine flow, myocardial function, and blood pressure, have not undergone profound deterioration. The shorter the time interval between onset of signs and symptoms and initiation of therapy with volume correction and dopamine hydrochloride, the better the prognosis.

Poor Perfusion of Vital Organs

Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. Nevertheless, the physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature, and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Clinical studies have shown that when dopamine hydrochloride is administered before urine flow has diminished to levels approximating 0.3 mL/minute, prognosis is more favourable. Nevertheless, in a number of oliguric or anuric patients, administration of dopamine hydrochloride has resulted in an increase in urine flow which in some cases reached normal levels. Dopamine hydrochloride may also increase urine flow in patients whose output is within normal limits and thus may be of value in reducing the degree of pre-existing fluid accumulation. It should be noted that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of dopamine hydrochloride and diuretic agents may produce an additive or potentiating effect.

Low Cardiac Output

Increased cardiac output is related to dopamine hydrochloride's direct inotropic effect on the myocardium. Increased cardiac output at low or moderate doses appears to be related to a favourable prognosis. Increase in cardiac output has been associated with either static or decreased systemic vascular resistance (SVR). Static or decreased SVR associated with low or moderate increments in cardiac output is believed to be a reflection of differential effects on specific vascular beds with increased resistance in peripheral beds (i.e., femoral) and concomitant decreases in mesenteric and renal vascular beds. Redistribution of blood flow parallels these changes so that an increase in cardiac output is accompanied by an increase in mesenteric and renal blood flow. In many instances, the renal fraction of the total cardiac output has been found to increase. Increase in cardiac output produced by dopamine hydrochloride usually is not associated with substantial decreases in systemic vascular resistance.

Hypotension

Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of dopamine hydrochloride, which have little effect on SVR. At high therapeutic doses, dopamine hydrochloride's alpha-adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. As in the case of other circulatory decompensation states, prognosis is better in patients whose blood pressure and urine flow have not undergone profound deterioration. Therefore, it is suggested that the physician administer dopamine hydrochloride as soon as a definite trend toward decreased systolic and diastolic pressures becomes evident.

CONTRAINDICATIONS

Dopamine hydrochloride should not be used in patients with pheochromocytoma.

Solutions containing dextrose may be contraindicated in patients with known allergy to corn or corn products.

WARNINGS AND PRECAUTIONS

General

Dopamine hydrochloride should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation.

DO NOT add dopamine hydrochloride to any alkaline diluent solution, since the drug is inactivated in alkaline solutions.

Patients who have been treated with monoamine oxidase (MAO) inhibitors prior to the administration of dopamine hydrochloride will require substantially reduced dosage.
Solutions containing dextrose should not be administered through the same administration set as blood, as this may result in pseudoagglutination or hemolysis. The intravenous administration of solutions may cause fluid overloading resulting in dilution of serum electrolyte concentrations, e.g. hypokalemia, overhydration, congested states or pulmonary edema.

Avoid bolus administration of dopamine hydrochloride. See DOSAGE AND ADMINISTRATION.

Extravasation
The infusion site should be frequently checked for free flow since several cases of necrosis and sloughing of surrounding tissue due to extravasation have been reported. Dopamine Hydrochloride and 5% Dextrose Injection, USP should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle. Less suitable infusion sites should be used only if the patient's condition requires immediate attention. The physician should switch to more suitable sites as rapidly as possible. The infusion site should be continuously monitored for free flow.

Cardiovascular

Dopamine hydrochloride, particularly when infused in high doses, may facilitate disturbances in impulse formation such as ectopic beats, tachycardia, sinus bradycardia and sinus arrhythmia. With the occurrence of these symptoms, dopamine hydrochloride should be used with extreme caution and, if necessary, the dosage should be reduced, or, if warranted, the infusion of dopamine hydrochloride should be stopped.

Avoid Hypovolemia
Prior to treatment with dopamine hydrochloride, hypovolemia should be fully corrected, if possible, with either whole blood plasma, or plasma expanders as indicated.

Decreased Pulse Pressure
If a disproportionate rise in the diastolic pressure (i.e., a marked decrease in the pulse pressure) or a decrease in urine flow is observed in patients receiving dopamine hydrochloride, the infusion rate should be decreased and the patient should be observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

IMPORTANT: Antidote for Peripheral Ischemia
No clinical experience exists in which phentolamine has been administered as an antidote for peripheral ischemia due to dopamine. However, the following is suggested based on experience with other catecholamines. To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 mL of 0.9% sodium chloride injection containing from 5 to 10 mg of phentolamine, an alpha-adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, phentolamine should be given as soon as possible after the extravasation is noted.

Peripheral Vasoconstriction
Several cases of severe vasoconstriction leading to vascular stasis and gangrene of the extremities have been reported after dopamine hydrochloride administration. Patients with pre-existing vascular disease such as cold injury, atherosclerosis, Raynaud's disease, diabetic endarteritis, seem to be particularly prone to severe peripheral vasoconstriction. Patients should be closely monitored for any changes in color or temperatures of the skin in the extremities. If a change in skin color or temperature occurs which is thought to be the result of compromised circulation to the extremities, the benefits of continued dopamine hydrochloride infusion should be weighed against the risk of possible necrosis. As noted above, phentolamine should be available on a standby basis as an antidote for peripheral vasoconstriction.

Endocrine and Metabolism

Solutions containing dextrose should be used with caution in patients with known subclinical or overt diabetes mellitus.

Immune

Sulfites Sensitivity
Dopamine Hydrochloride and 5% Dextrose Injection contains sodium bisulfite, a sulfite that may cause allergic-type reactions including anaphylactic reactions symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown, and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Respiratory

The administration of dopamine hydrochloride in patients with primary pulmonary hypertension can cause pulmonary vasoconstriction which may be detrimental to the condition of these patients.

Special Populations

Pregnant Women: Animal studies have revealed no evidence of teratogenic effects from dopamine hydrochloride. The drug may be used in pregnant women when, in the judgment of the physician, the expected benefits outweigh the potential for risk to the fetus.

Nursing Women: It is not known whether dopamine is excreted in human milk.

Pediatrics: The safety and efficacy of this drug in children has not been established. Dopamine hydrochloride has been used in a limited number of pediatric patients, but such use has been inadequate to fully define proper dosage and limitations for use.

Monitoring and Laboratory Tests

Close monitoring of the following indices -- urine flow, cardiac output and blood pressure -- during dopamine hydrochloride infusion is necessary as in the case of any adrenergic agent.

Do not administer unless solution is clear and seal is intact. If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result.

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation.

ADVERSE REACTIONS

The most serious adverse reactions produced by dopamine hydrochloride are ventricular arrhythmia and atrial fibrillation.

MedDRA Term	Most Frequent Adverse Reactions Observed in Clinical Evaluation	Other Reactions Reported Infrequently
Cardiovascular System	ectopic beats tachycardia palpitation anginal pain hypotension vasoconstriction	aberrant conduction bradycardia widened QRS complex elevated blood pressure
Respiratory System	dyspnea	bronchospasm
Gastrointestinal System	nausea vomiting	
Metabolic/Nutritional System		azotemia
Central Nervous System	headache	
Dermatological System		piloerection

Extravasation

Sloughing and necrosis of surrounding tissue due to extravasation when dopamine hydrochloride was infused into small veins has been reported.

Peripheral Vasoconstriction

Peripheral ischemic changes leading to vascular stasis and gangrene have been reported. Patients with pre-existing vascular disease may be particularly sensitive to the vasoconstrictive effects of dopamine hydrochloride (see PRECAUTIONS).

Other Reactions

Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of extravasation and hypervolemia.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

DRUG INTERACTIONS

Dopamine is metabolized by MAO, and inhibition of this enzyme prolongs and potentiates the effect of dopamine hydrochloride. The starting dose in such patients should be reduced to at least one-tenth (1/10) of the usual dose.

Cyclopropane or halogenated hydrocarbon anesthetics increase cardiac autonomic irritability and therefore seem to sensitize the myocardium to the action of certain intravenously administered catecholamines. Dopamine hydrochloride should be used with extreme caution in patients inhaling cyclopropane or halogenated hydrocarbon anesthetics.

When dopamine hydrochloride is administered concurrently with diuretics, extra caution should be taken because it may produce an additive or potentiating effect.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dopamine Hydrochloride and 5% Dextrose Injection is a premixed ready-to-use solution. No further dilution is recommended. No other drugs should be added to this solution.

Recommended Dose and Dosage Adjustment

Rate of Administration

Dopamine Hydrochloride and 5% Dextrose Injection, USP is administered intravenously through a suitable intravenous catheter or needle. An IV drip chamber or other suitable metering device is essential for controlling the rate of flow in drops/minute. Each patient must be individually titrated to the desired hemodynamic and/or renal response with dopamine hydrochloride.

In titrating to the desired increase in systolic blood pressure, the optimum dosage rate for renal response may be exceeded, thus necessitating a reduction in rate after the hemodynamic condition is stabilized.

Administration of dopamine hydrochloride at rates greater than 50 µg/kg/min have safely been used in advanced circulatory decompensation states. If unnecessary fluid expansion is of concern, use of a more concentrated solution may be preferred over increasing the flow rate of a less concentrated solution.

Suggested Regimen

1. When appropriate, increase blood volume with whole blood, plasma, or plasma expanders until central venous pressure is 10 to 15 cm H_20 or pulmonary wedge pressure is 14 to 18 mm Hg.

2. Begin infusion of Dopamine Hydrochloride and 5% Dextrose Injection, USP at doses of 2 to 5 µg/kg/min in patients who are likely to respond to modest increments of heart force and renal perfusion.

   In more seriously ill patients, begin administration of Dopamine Hydrochloride and 5% Dextrose Injection, USP at rates of 5 µg/kg/min and increase gradually using 5 to 10 µg/kg/min increments up to a rate of 20 to 50 µg/kg/min as needed. If rates in excess of 50 µg/kg/min are required, it is suggested that urine output be checked frequently.

   Should urine flow begin to decrease in the absence of hypotension, reduction of dopamine hydrochloride dosage should be considered. Reports have shown that more than 50% of the patients were satisfactorily maintained on doses of dopamine hydrochloride administered at rates of less than 20 µg/kg/min. In patients who do not respond to these doses with adequate arterial pressures or urine flow, additional increments of dopamine hydrochloride may be given in an effort to produce an appropriate arterial pressure and central perfusion.

3. Treatment of all patients requires constant evaluation of therapy in terms of blood volume, augmentation of myocardial contractility, and distribution of peripheral perfusion. Dosage of dopamine hydrochloride should be adjusted according to the patient's response with particular attention to diminution of established urine flow rate, increasing tachycardia or development of new dysrhythmias as indices of decreasing or temporarily suspending the dosage.

4. As with all potent intravenously administered drugs, care should be taken to control the rate of administration so as to avoid inadvertent administration of a bolus of drug.

Administration

Dopamine Hydrochloride and 5% Dextrose Injection, USP should be inspected visually for particulate matter and discoloration prior to administration.

Do not use these injections if they are darker than slightly yellow or discolored in any other way.

All injections in VIAFLEX plastic containers are intended for intravenous administration using sterile equipment. The solution is intended for single use only. When smaller doses are required, the unused portion should be discarded.

Directions for Use of Viaflex Plastic Containers

Dopamine Hydrochloride and 5% Dextrose Injection is a premixed ready-to-use solution. No further dilution is recommended. No other drugs should be added to this solution.

Do not remove unit from overwrap until ready to use.

To Open:
Tear overwrap down side at notch and remove solution container. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

Preparation for Administration:
CAUTION:
Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is completed.

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

OVERDOSAGE

In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce the rate of administration or temporarily discontinue dopamine hydrochloride until patient's condition stabilizes. Since dopamine hydrochloride's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha-adrenergic blocking agent, phentolamine, should be considered.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Dopamine hydrochloride exerts an inotropic effect on the myocardium resulting in an increased cardiac output. Dopamine hydrochloride produces less increase in myocardial oxygen consumption than isoproterenol and its use is usually not associated with tachyarrhythmia. Clinical studies indicate that dopamine hydrochloride at low and intermediate therapeutic doses usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure, and total peripheral resistance is usually unchanged.

Blood flow to peripheral vascular beds may decrease while mesenteric flow increases. Dopamine hydrochloride has also been reported to dilate the renal vasculature presumptively by activation of a "dopaminergic" receptor. This action is accompanied by increases in glomerular filtration rate, renal blood flow, and sodium excretion. An increase in urinary output produced by dopamine is usually not associated with a decrease in osmolarity of the urine.

Pharmacokinetics

Dopamine hydrochloride is a rapidly-acting compound. Cardiovascular effects are usually evident within 10 minutes, and renal response usually occurs within 30 minutes.

The half-life of dopamine is approximately 1.75 minutes.

STORAGE AND STABILITY

It is recommended the product be stored at room temperature (15-25°C): brief exposure up to 40°C does not adversely affect the product. Avoid excessive heat. Protect from light and freezing.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dopamine Hydrochloride and 5% Dextrose Injection, USP in VIAFLEX plastic container is available in different sizes and concentrations as listed in Table 1.

Table 1

	COMPOSITION*					
	Diluent Volume (mL)	Dopamine Hydrochloride, USP (µg/mL)	Dextrose Hydrous USP (g/L)	Approx. Osmolarity mOsmol/L	pH Range	Approx kcal/L
200 mg Dopamine Hydrochloride and 5% Dextrose Injection, USP	250	800	50	270	2.5 to 4.5	170
400 mg Dopamine Hydrochloride and 5% Dextrose Injection, USP	250	1600	50	280	2.5 to 4.5	170

800 mg Dopamine Hydrochloride and 5% Dextrose Injection, USP	250	3,200	50	300	2.5 to 4.5	170
	500	1,600	50	280	2.5 to 4.5	170

*Approximately 5 mEq/L sodium bisulfite is added as a stabilizer; pH is adjusted with hydrochloric acid.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

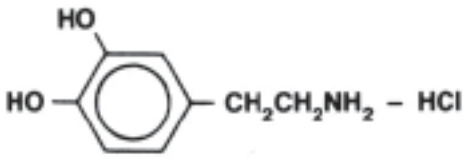
Proper name: Dopamine Hydrochloride

Chemical name: 3,4-dihydroxyphenethylamine hydrochloride

Molecular formula: $C_8H_{11}NO_2.HCl$

Molecular mass: 189.64

Structural formula:



Physicochemical properties: Dopamine hydrochloride is a white, odorless, crystalline powder, soluble in water and alcohol with a melting point range of 240° to 248°C (with decomposition). It is sensitive to light, alkalis, iron salts and oxidizing agents.

DETAILED PHARMACOLOGY

Cardiovascular Effects

In anesthetized dogs, dopamine possesses about 1/60 the pressor activity of norepinephrine and 1/28 the pressor activity of epinephrine as determined by the dose necessary to induce a 25% increase in systolic pressure (i.e., ED25). This ED25 dose of dopamine (33 µg/kg/minute), however, caused only a 4% rise in diastolic pressure. Throughout the dosage range of 25 to 200 µg/kg/minute, there was no significant change in the heart rate.

At low to moderate doses of dopamine (1-25 µg/kg/minute), the increase in systolic pressure in dogs is due primarily to increased myocardial contractile force resulting in an improvement in stroke volume and cardiac output. At dosages exceeding 50 µg/kg/minute, pressure and peripheral resistance are simultaneously elevated.

In anesthetized marmoset monkeys, the effect on blood pressure of 5-minute dopamine infusions in dosage rates ranging from 6.25 to 800 µg/kg/minute was dosage dependent. At dosages ranging up to 50 µg/kg/minute, reductions in systolic pressure of the order of 12 to 23 percent were noted, while increases in pressure were apparent at dosages between 100 and 800 µg/kg/minute. As was the case in dogs, the effects on heart rate were minimal and insignificant.

Although dopamine is the direct physiological precursor of norepinephrine, a variety of studies have demonstrated that the effects of exogenous dopamine appear to be primarily attributable to dopamine. Pre-treatment of rats with disulfiram, an inhibitor of dopamine b-hydroxylase, did not modify the cardiovascular response to dopamine. In reserpinized rats, the cardiovascular effects of tyramine, an indirect-acting catecholamine, were abolished, while the effects of dopamine were not reduced and, in fact, were somewhat potentiated. Pre-treatment of rats with both reserpine and disulfiram did not significantly alter the response to dopamine.

Renal Effect

Dopamine is unusual relative to other clinically employed catecholamines in that it consistently increases renal blood flow (RBF) and urine production. In anesthetized dogs, urine flow was increased up to 375% in dosages ranging up to 15 µg/kg/minute. At higher doses, the incremental increase was lower in magnitude. Low and moderate doses of dopamine in both dog and human result in increased RBF and decreased renal resistance.

Single intrarenal injections of high doses of dopamine in dogs (24 and 48 µg) produced a biphasic renal response characterized by a brief initial decrease in RBF due to vasoconstriction, followed by a more sustained increase in RBF. At higher doses the constrictor component was more prominent, and, in fact, RBF was reduced below control levels.

The reduction in RBF, GFR and urine flow caused by high doses of dopamine was completely inhibited by the alpha-adrenergic blocking agent, phentolamine, and partially inhibited by the beta-adrenergic blocking agent, propranolol. Neither alpha nor beta blockers, however, were capable of modifying the renal vasodilator component of action of dopamine.

In doses of 6 µg/kg/minute, dopamine increased sodium clearance and raised GFR by 11% in anesthetized and unanesthetized dogs. These effects are not entirely secondary to systemic hemodynamic effects of dopamine as demonstrated by an ipsilaterally greater augmentation of GFR as well as PAH and sodium clearance following unilateral injection of dopamine into the renal artery of dogs. The intimate site of natriuretic action of dopamine in the nephron has not been verified. Both the proximal tubule and the distal tubule have been implicated.

Effects on Mesenteric and Celiac Blood Flow

Both mesenteric and celiac vasodilation can be produced by dopamine in the anesthetized dog and cat. As in the renal vascular bed, adrenergic blocking agents were incapable of inhibiting this vasodilation.

TOXICOLOGY

Acute Toxicity

Acute 24-hour LD50 determinations utilizing single doses of dopamine were conducted in mice, rats, rabbits, and dogs. The following data were obtained:

Mice, male, LD50 p.o. = 2075 ± 81.5 mg/kg*
Mice, male, LD50 s.c. = 1950 ± 133 mg/kg*
Mice, male, LD50 i.p. = 970 ± 74 mg/kg*
Mice, male, LD50 i.v. = 290 ± 14 mg/kg*

Rats, male, LD50 p.o. = 2800 ± 140 mg/kg*
Rats, male, LD50 s.c. = 2575 ± 215 mg/kg*
Rats, male, LD50 i.p. = 1015 ± 87.5 mg/kg*
Rats, male, LD50 i.v. = 38.8 ± 6.15 mg/kg*

Rabbits, male, approx. LD50 i.v. = 125 – 150 mg/kg

Dogs, random sex, approx. LD50 i.v. = 75 – 100 mg/kg

*LD50 ± confidence limits

Gross post-mortem studies of non-surviving animals from these studies revealed pulmonary congestions and massive internal hemorrhage. Surviving animals, as well as those which ultimately died, exhibited excessive lacrimation, salivation, and exophthalmus.

Subacute toxicity

Male and female rats were subject to daily i.p. doses of dopamine ranging from 25 to 570 mg/kg/day for 14 days. Normal behaviour, appetite, bowel habits, sensoria, and growth patterns were maintained in all groups.

Statistically significant increases in kidney, liver, heart and lung weights were noted in all groups receiving 570 mg/kg/day. At a daily dosage of 285 mg/kg/day, heart, kidney, and adrenal weights increased, while spleen weight decreased. Heart and adrenal weights increased in female rats at a dosage of 143 mg/kg/day. Statistically significant increases in the heart weights of female rats receiving 50 and 25 mg/kg/day were noted. Adrenal weight also increased in female rats receiving 25 mg/kg/day. No significant changes in organ weights occurred in either sex at a dosage of 100 mg/kg/day.

Histopathological examination revealed marked prostatic enlargement with secondary hydronephrosis in male rats receiving dopamine doses in excess of 143 mg/kg/day. No other histopathological changes were observed. No drug-related aberrancies were noted in hematological studies and in blood chemistry.

Two subacute studies were conducted in dogs. In the first study, dopamine was given i.v. in doses of 18.75, 37.5 and 75 µg/kg/minute for one hour on each of 14 consecutive days. The only overt signs of toxicity were excessive salivation and occasional emesis. These appeared to be dose-related. Hematology, urinalysis and blood chemistry, as well as gross and microscopic anatomy, were unaltered. No drug-related pathology was observed.

The second subacute dog study involved continuous i.v. administration of dopamine to dogs in doses of 9.4, 18.8 and 37.5 µg/kg/minute for 24 hours a day over a period of 14 days.
Adrenal weights were significantly elevated over saline controls in all three drug-related groups. Spleen weights were elevated at the two higher doses, while the prostates in the intermediate group were decreased in weight. These changes appeared to be dose-related.

Tiny, focal myocardial lesions were apparent in 5/6 of the animals maintained at the high dose, while 1/6 dogs at the intermediate dose exhibited these lesions.

Heart weights upon autopsy were lower than control in the intermediate dosage group and lung weights were lower than control in the intermediate and low-dose groups.

All groups, including saline controls, exhibited a small decrease in weight between the beginning and termination of the experiment. This difference was significant only in the high dose group.

No drug-related changes were noted in hematology, blood chemistry, or urinalysis in these animals. In particular, serum and urine osmolality were unchanged.

REFERENCES

1. Trissel LA. Handbook on injectable drugs, fourth edition. Amer Soc of Hosp Pharm 1986.
2. Goodman and Gilman. The pharmacological basis of therapeutics, seventh edition. MacMillan Publishing Co 1985.
3. Vetrovec GW, Hess ML. Hemodynamic effects of dopamine administration in patients with severe chronic congestive heart failure: comparison of two dopamine products. Curr Ther Res Clin Exp 1983;34(Jul):153-163.
4. Ruiz CE, et al. Treatment of circulatory shock with dopamine: studies on survival. J Am Med Assoc 1979; 242(Jul):165-168.
5. Goldberg LI. Cardiovascular and renal actions of dopamine: potential clinical applications. Pharmacol Rev 1972; 24(1):1-29.
6. Rosenblum R, et al. Dopamine in man: cardiorenal hemodynamics in normotensive patients with heart disease. J Pharmacol and Exp Ther 1972; 183(2):256-263.
7. Rosenblum R, Frieden J. Intravenous dopamine in the treatment of myocardial dysfunction after open heart surgery. Amer Heart J 1972;83(6):743-748.
8. Loeb HS, et al. Acute hemodynamic effects of dopamine in patients with shock. Circ 1971;XLIV:163.
9. Zaroslinski JF, Brown RK. Effects of dopamine on canine renal artery. The Pharmacologist 1971;13(2):227.
10. Talley RC, et al. Reversal of acute renal failure with a combination of intravenous dopamine and diuretics. Clin Res 1970;18:518.
11. Goldberg LI, et al. Potential role of dopamine in the treatment of shock. Progr Cardiovas Dis 1969;21(1):40.
12. Talley RC, et al. A hemodynamic comparison of dopamine and isoproterenol in patients in shock. Circ 1969;XXXIX:361.

13. Goodall McC, Alton H. Dopamine (3-hydroxytyramine) metabolism in parkinsonism. J Clin Invest 1969;48(12):2300.

14. Datz RL, et al. Anesthetic-dopamine cardiac arrhythmias and their prevention by beta adrenergic blockade. J Pharmacol and Exp Ther 1967;158(1):40-45.

15. Weber LJ. Drug interactions between disulfiram and a-methyldopa and related agents in reserpine-pretreated rats. Proc Soc Exp Biol Med 1966;123:349-352.

16. MacCannell KL, et al. Dopamine in the treatment of hypotension and shock. New Eng J Med 1966;275(Dec 22):1389-1398.

17. McNay JL, et al. Direct renal vasodilation produced by dopamine in dogs. Cir Res 1965;XVI:510-517.

18. Katz RL. Effects of alpha and beta adrenergic blocking agents on cyclopropane-catecholamine cardiac arrhythmias. Anesthesiology 1965;26(3):289-298.

19. Allwood MJ, Ginsburg J. Peripheral vascular and other effects of dopamine infusions in man. Clin Sci 1964;27:271.

20. MacDonald RH Jr, et al. Effects of dopamine in man: augmentation of sodium excretion, glomerular filtration rate, and renal plasma flow. J Clin Invest 1964;43(6):116,.

21. Goldberg LI, et al. Sodium diuresis produced by dopamine in patients with congestive heart failure. New Eng J Med 1963;269(Nov 14):1060-1064.

PART III: CONSUMER INFORMATION

DOPAMINE HYDROCHLORIDE AND 5% DEXTROSE INJECTION, USP

Dopamine Hydrochloride 800, 1600, and 3200 µg/mL and 5% Dextrose in VIAFLEX Plastic Container

This leaflet is part III of a three-part "Product Monograph" published when Dopamine Hydrochloride and 5% Dextrose Injection, USP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Dopamine Hydrochloride and 5% Dextrose Injection, USP. Contact your doctor, nurse or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Dopamine Hydrochloride and 5% Dextrose Injection, USP may be used to increase low blood pressure in people who have:

- experienced a heart attack;
- lost blood during an accident;
- a severe infection;
- kidney failure;
- problems after surgery.

Dopamine Hydrochloride and 5% Dextrose Injection, USP may be used in people with congestive heart failure to help the heart pump better.

What it does:

Dopamine Hydrochloride and 5% Dextrose Injection, USP acts to increase the blood flow to the muscles and can increase the heart's pumping efficiency. Dopamine Hydrochloride and 5% Dextrose Injection, USP also increases blood flow to the kidneys.

When it should not be used:

Dopamine Hydrochloride and 5% Dextrose Injection, USP should not be given to patients with:

- allergies to dopamine hydrochloride, dextrose or any non-medicinal ingredient in the formulation or components of the VIAFLEX Plastic container;
- are sensitive to sulfites;
- adrenal gland tumour (pheochromocytoma);
- irregular heart beat (arrhythmia).

The solution contains dextrose and should not be used in patients with known allergy to corn or corn products.

What the medicinal ingredient is:

Dopamine hydrochloride

What the nonmedicinal ingredients are:

Dextrose, Sodium bisulfite.

What dosage forms it comes in:

Solution for intravenous injection 800 µg/mL, 1600 µg/mL and 3200 µg/mL

WARNINGS AND PRECAUTIONS

BEFORE you are given Dopamine Hydrochloride and 5% Dextrose Injection, USP talk to your doctor, nurse or pharmacist if you have:

- hardening of the blood vessels
- Raynaud's disease, where the fingers become white and very painful when cold
- diabetes
- frostbite
- high blood pressure
- been treated with monoamine oxidase (MAO) inhibitors for depression

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with Dopamine Hydrochloride and 5% Dextrose Injection, USP :

- some antidepressants (MAO inhibitors, tricyclic antidepressants)
- certain anesthetic agents used during surgery
- diuretic agents (“water pills”)
- some drugs used to treat high blood pressure and prevent the symptoms of angina (chest pain)
- some drugs used to treat psychiatric disorders
- drugs used to stop bleeding (such as ergonovine) and some oxytocic drugs (drugs used during labour)
- drugs used to control seizures, such as phenytoin

PROPER USE OF THIS MEDICATION

Usual dose:

Your doctor will decide what dose you will receive. This depends on your condition and other factors, such as your weight.

Overdose:

Dopamine Hydrochloride and 5% Dextrose Injection, USP is an intravenous (IV) drug given to you in hospital under the supervision of your doctor, so it is very unlikely that you will receive an overdose. An overdose could raise blood pressure too high.

In case of drug overdose, your doctor will reduce the amount or temporarily stop giving it to you. In some cases, your doctor may give you another drug to reduce your blood pressure.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

If you do not feel well while you are being given Dopamine Hydrochloride and 5% Dextrose Injection, USP or soon after the injection, tell your doctor, nurse or pharmacist as soon as possible.

Side effects may include:

- nausea
- vomiting
- headache
- anxiety

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor, nurse or pharmacist		Stop taking drug and seek immediate medical help
		Only if severe	In all cases	
Common	chest pain			√
	irregular or rapid heart beat			√
	low blood pressure / dizziness		√	
Uncommon	blood circulation problem / cold or tingling feet		√	
	difficulty breathing			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor, nurse or pharmacist		Stop taking drug and
Unknown	fever, irritation/infection at the injection site;		√	
	Venous Thrombosis (blood clot) or Phlebitis (inflammation of the vein): swelling, hard cord-like vein, redness, warmth and pain in the arm near the injection site;			√
	Allergic Reaction: rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing			√

This is not a complete list of side effects. For any unexpected effects after administration of Dopamine Hydrochloride and 5% Dextrose Injection, USP, speak with your doctor or pharmacist.

HOW TO STORE IT

Dopamine Hydrochloride and 5% Dextrose Injection, USP is stored at room temperature (15-25°C), protected from light and freezing.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Baxter Corporation at:
1-800-387-8399

This leaflet was prepared by Baxter Corporation.

Last revised: April 24, 2013.